(a) administering to a mammal at risk of sepsis-associated lethality an amount of isolated or purified tissue cytotoxic factor – II (TCF-II) effective to reduce sepsis-associated lethality.

3. (Amended) The method of claim 2, wherein the TCF-II is administered intravenously, intramuscularly or subcutaneously.

13. (Amended) A method for reducing bacterial translocation in a mammal, the method comprising the step of:

(a) administering to a mammal at risk of bacterial translocation in the intestine an amount of isolated or purified tissue cytotoxic factor – II (TCF-II) effective to reduce bacterial translocation.

14. (Amended) The method of claim 13, wherein the TCF-II is administered intravenously, intramuscularly or subcutaneously.

REMARKS

Claims 2-23 were pending. Claims 2, 3, 13, and 14 are amended, and claims 12 and 23 are cancelled by the present amendment. Accordingly, claims 2-11 and 13-22 are pending and presented for reconsideration.

Claim 2 is amended to recite a method for reducing sepsis-associated lethality comprising administering, to a mammal at risk of sepsis-associated lethality, an amount of isolated or purified tissue cytotoxic factor – II (TCF-II) effective to reduce sepsis-associated lethality. Support for the amendment to claim 2 is found throughout the originally-filed application and at least, for example, at pages 4-6 and 8-9, and in Figure 1.

Claim 13 is amended to recite a method for reducing bacterial translocation, comprising administering, to a mammal at risk of bacterial translocation in the intestine, an amount of isolated or purified tissue cytotoxic factor – II (TCF-II) effective to reduce bacterial translocation. Support for the amendment to claim 13 is found throughout the originally-filed application and at least, for example, at pages 4-6 and 8-9, and in Figure 2.

Claims 3 and 14 are amended to correct antecedent basis.

Applicants submit that the amendments introduce no new matter.

Objections to the Drawings

Applicants enclose formal drawings to address the objections to the drawings. In view of the newly-submitted drawings, Applicants request that the objection to the drawings be withdrawn.

Information Disclosure Statement

According to the Office action, "copies of the crossed out references on page 4 of the IDS were not provided." References CAC, CAD, and CAH were crossed out; reference CAJ was neither crossed out nor initialed. Applicants note that the USPTO acknowledged receiving each of these four references on August 3, 2001, as indicated by the attached copy of the date-stamped postcard from the USPTO. Applicants enclose substitute copies of references CAH and CAJ and a substitute 1449 form listing them. Applicants believe no fee is required, as these are merely courtesy copies of references previously provided to the USPTO. If a fee is required, please charge deposit account no. 20-0531. Applicants respectfully request that each of the references be considered and that the corresponding entries on the substitute 1449 form be initialed.

Claim rejections under 35 U.S.C. § 112

Claims 4 and 15 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter insufficiently described in the specification.

Applicants traverse this rejection. Claims 4 and 15 are directed to methods for preventing or treating sepsis in a mammal. The methods include "expressing a recombinant DNA encoding TCF-II in a host cell." Descriptions of recombinant DNA expression are found throughout the application: see, for example, the paragraph bridging pages 3 and 4: "TCF-II as an effective ingredient of the present invention can be . . . TCF-II genetically engineered using microorganism or other cell lines based on the genetic sequence described in patent publication WO90/10651. TCF-II obtained by genetically engineered manipulation described in patent publication WO92/01053 can also be used. In such a case, TCF-II with different polysaccharide chain or without polysaccharide chain due to the difference of host cell or microorganism can be used . . . ." The Examples further disclose expression of TCF-II in IMR-90 human fibroblast cells and in transformed Namalwa cells. Applicants submit that the application describes expression of recombinant DNA encoding TCF-II in host cells and request reconsideration and withdrawal of this rejection.

Claims 2-11 and 13-22 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabling the full scope of the claims. The Office action acknowledged that the specification enables "a method of increasing the survival rate of sepsis in a mammal by decreasing lipopolysaccharide (LPS)-induced bacterial translocation in the intestine comprising administering to the mammal an amount of isolated or purified tissue cytotoxic factor – II (TCF-II) sufficient to decrease LPS-induced bacterial translocation in the intestine thereby increasing the survival rate of sepsis." As amended, the pending claims relate to methods of reducing sepsis-associated lethality (claim 2) or reducing bacterial translocation (claim 13) in a mammal, comprising administering an amount of isolated or purified tissue cytotoxic factor – II (TCF-II) effective to reduce sepsis-associated lethality (claim 2) or bacterial translocation (claim 13). Applicants traverse the rejection to the extent it is maintained against the amended claims.

Sepsis, as indicated at page one of the application and as acknowledged in the Office action, is a systemic disease associated with invasion of bacteria or bacterial products into the blood. As indicated at page two of the application, bacteria are thought

to invade through tissue puncture and/or through bacterial translocation. The Examples demonstrate the effectiveness of TCF-II both when the cecum is punctured (Figure I) and in LPS-induced bacterial translocation (Figure II).

Applicants submit that the specification enables the reduction of sepsis-associated lethality, regardless of the route of infection. The application teaches that TCF-II is effective in reducing lethality when the cecum is punctured, rupturing the physical barrier that prevents systemic invasion by intestinal flora. Once bacteria have invaded the bloodstream, prognosis should be determined by their presence and action in the blood, not their route of invasion. Thus, TCF-II is expected to be effective in treating sepsis regardless of the triggering event (*e.g.* "burn, surgery, cancer, AIDS, radiotherapy, chemotherapy and long term TPN," as taught at page 3 of the application). Furthermore, the application teaches pharmaceutical preparations useful in treating sepsis at pages 6-8 and useful dosages and modes of administration at page 4. Applicants submit that no more than routine experimentation would be necessary to verify the effectiveness and appropriate dosage of TCF-II in reducing sepsis-associated lethality triggered by other events.

The specification similarly enables the reduction of bacterial translocation. Example II demonstrates that TCF-II significantly suppresses LPS-induced translocation of bacteria from intestine; Applicants submit that routine experimentation would be sufficient to verify the effectiveness and appropriate dosage for reducing bacterial translocation caused by other triggers such as immunodeficiencies, burns, or total parenteral nutrition.

Applicants respectfully request reconsideration and withdrawal of this rejection to the extent it is maintained over the amended claims.

Claims 4 and 15 are also rejected under 35 U.S.C. § 112, first paragraph, as not enabled because they allegedly recite "the administration of cells producing TCF-II." Applicants submit that the claims do not recite the administration of cells; rather, the claims recite "expressing a recombinant DNA encoding TCF-II in a host cell." Thus, the

invention of claims 4 and 15 relates to recombinant expression systems useful for production of TCF-II, not to cell administration. Accordingly, Applicants request reconsideration and withdrawal of this rejection.

Claims 11 and 12 (probably intended as 11 and 22) also stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled for failure of the application to describe "how to modify any polysaccharide chain attached to TCF-II," and under 35 U.S.C. § 112, second paragraph, as "apparently redefin[ing] TCF-II as a polysaccharide chain." Applicants traverse these rejections. Claims 11 and 22 do not redefine TCF-II as a polysaccharide chain. TCF-II is a polypeptide. When synthesized recombinantly, the choice "of host cell or microorganism" will affect the presence or absence and character of any glycosylation patterns, as described at page 4 of the application. Claims 11 and 22 specify methods in which the TCF-II is glycosylated: the TCF-II "comprises a polysaccharide chain." Applicants submit that the metes and bounds of the claims are clear, as required by 35 U.S.C. § 112, second paragraph. Furthermore, as the application describes various TCF-II production methods leading to the synthesis of glycosylated TCF-II, Applicants submit that the claims comply with 35 U.S.C. § 112, first paragraph. Applicants respectfully request reconsideration and withdrawal of these rejections.

Claims 2-11 and 13-22 stand rejected under 35 U.S.C. § 112, second paragraph, because the first use of the acronym "TCF-II" in the claims was not preceded by its full name. Applicants have amended both independent claims to recite "tissue cytotoxic factor – II (TCF-II). Applicants request reconsideration and withdrawal of this rejection.

Claims 2-11 stand rejected under 35 U.S.C. § 112, second paragraph, because the word "treatment" is allegedly indefinite. Applicants have amended the claims to remove the word "treatment." Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 2-11 stand rejected under 35 U.S.C. § 102(a) as allegedly anticipated by WO 98/41230 and WO 98/40096. As noted by the Office action, the publication dates of these references do not predate Japanese patent application JP 10/70914, filed March 19,

1998, to which the present application claims priority under 35 U.S.C. §§ 365(b) and 119(a). Applicants enclose herewith a certified English translation of the Japanese priority document. Applicants submit that the claims are entitled to the March 19, 1998, priority date, and respectfully request reconsideration and withdrawal of the rejections.

CONCLUSION

Claims 2-11 and 13-22 are pending and presented for consideration. The Examiner is invited to contact the undersigned to discuss any outstanding issues.

Respectfully submitted,

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MARKED-UP COPY OF THE AMENDED CLAIMS

2. (Amended) A method for [treating] reducing sepsis-associated lethality in a mammal, the method comprising the step of:

(a) administering to [the] a mammal at risk of sepsis-associated lethality an amount of isolated or purified tissue cytotoxic factor – II (TCF-II) effective to [treat] reduce sepsis-associated lethality.

3. (Amended) The method of claim 2, wherein the [therapeutic agent] TCF-II is administered intravenously, intramuscularly or subcutaneously.

13. (Amended) A method for [preventing sepsis] reducing bacterial translocation in a mammal, the method comprising the step of:

(a) administering to [the] a mammal at risk of bacterial translocation in the intestine an amount of isolated or purified tissue cytotoxic factor – II (TCF-II) effective to [prevent sepsis] reduce bacterial translocation.

14. (Amended) The method of claim 13, wherein the [therapeutic agent] TCF-II is administered intravenously, intramuscularly or subcutaneously.